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| EXAMINER | |
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| JEAN-LOUIS, SAMIRA JM | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/525,736 | LULLA ET AL. | |
| | Examiner | Art Unit | |
| | SAMIRA JEAN-LOUIS | 1627 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *20 July 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-9,15-26 and 34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 15-26, and 34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Response to Arguments*

This Office Action is in response to the amendment submitted on 07/20/10. Claims 1-9, 15-26, and 34 are currently pending in the application, with claims 10-14 and 27-33 having being cancelled. Accordingly, claims 1-9, 15-26, and 34 are being examined on the merits herein.

Receipt of the aforementioned amended claims is acknowledged and has been entered.

Applicant's argument with respect to the Obviousness Double Patenting (ODP) rejection has been fully considered. Applicant argues that because the conflicting claims have not been patented, the ODP rejection and terminal disclaimer are inappropriate. Such arguments are not found persuasive as the Examiner maintains that the instant claims are indeed rendered obvious by co-pending application in view of Meade. Lulla '902 (i.e. co-pending application 11/574,902) teaches a composition comprising salmeterol and tiotropium. While Lulla '902 does not teach addition of corticosteroids, Meade teaches the combination of salmeterol and tiotropium in combination with a corticosteroid such as fluticasone for the treatment of COPD. As a result, the Examiner maintains that one of ordinary skill in the art would have found it obvious to add fluticasone to the composition of Lulla '902 if the desire is to formulate a

composition for the treatment of COPD. As a result, the Examiner continues to maintain that the instant claims are indeed rendered obvious over Lulla '902 in view of Meade.

Applicant's arguments against the 103(a) rejection over Meade in view of Foulds have been fully considered. Applicant argues that in view of the amendments, present claims 1-9, 15-26, and 34 are now patentable over Meade in view of Foulds. Moreover, Applicant argues that independent claim 34 possess a structural feature and recite limitations that require particular dosage forms which overcome the teachings of the prior art. Such arguments are however not found persuasive as the Examiner contends that applicant is arguing newly added claims that have yet to be examined. It is noted that the features upon which applicant relies (i.e., particular particulate dosage forms) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Consequently, such arguments are moot. The Examiner again reminds applicant that the instant invention was directed to a pharmaceutical composition or product comprising a combination of therapeutic agents as a combined preparation for the treatment of inflammatory and respiratory diseases wherein the therapeutic agents are provided in particulate forms and wherein approximately 95% of the active particles have a particle size of below 2.5 μm and the remaining particles have a particle size between 2.5 and 5 μm. While applicant argues that the claims recite the use of specific dosage forms, the Examiner reminds applicant that the claims as previously recited do not require that the

composition be solid. As a result, the Examiner contends that because Meade teaches the combination of anticholinergics such as titropium, corticosteroids such as fluticasone, and beta-mimetics such as salmeterol as inhalable powders and aerosols and inhalable solutions with particulate size between 1 and 5 μm and because Foulds teaches that particle sizes play a role in the performance of particle delivery to the lungs one skilled in the art would have found it obvious to formulate the particles of the aforementioned therapeutic agents in small sizes if the desire is to provide an efficient way of delivering the active substances to the respiratory tract.

As for applicant's argument that Meade does not explicitly teach a combination of the aforementioned pharmaceutical product and that Foulds is directed to nebulizers, such arguments are not persuasive as the Examiner contends that the claims were not anticipated but rather rendered obvious. Moreover, the claims as recited do not teach a particular dosage formulation but rather that the combination product or composition needed to contain particulates. Thus, given that nebulizers entails suspensions (i.e. liquids containing particulates) and given that Meade teaches the combination of anti-cholinergics, beta-mimetics, and corticosteroids and cites tiotropium, salmeterol, and fluticasone as examples of such therapeutic agents that can be combined, the Examiner maintains that Meade in view of Foulds did indeed render obvious applicant's invention. As for the particle size, the Examiner refers applicant to Meade who teaches that the active substances are preferably an average particle size from 1 to 5 μm (see pg. 6, paragraphs 0036 and 0045). Since Meade is silent on the percentage of particles that possess the aforementioned particle size, the Examiner provided a technical reasoning

that 100% of the particles must consequently possess an average particle size of 1 to 5 μm. Further, the Examiner reminds applicant that sound technical and scientific reasoning can be used to support a conclusion of common knowledge and thus the Examiner maintains that no unfounded assumptions or hindsight reconstruction were proffered by the Examiner.

Applicant's argument with respect to the 1.132 Declaration/Affidavit has again been fully considered but is not found persuasive. Applicant argues that as compared to single or double combinations, the claimed triple active agent combinations exhibit unexpected reduction in agglomeration whereas liquids (as taught by Foulds) do not agglomerate. Such arguments are not persuasive as the Examiner maintains that the claims as recited (other than claim 34) do not require the pharmaceutical product or composition to be a solid and thus such arguments are moot. Additionally, the Examiner maintains that reduction in agglomeration is not unexpected as Meade clearly teaches the triple combination of betamimetics such as salmeterol, anticholinergics such as tiotropium, and corticosteroids such as fluticasone for the treatment of COPD. Additionally, Meade teaches that the active substances have a preferred average particle size of 0.5 to 10 μm and most preferably particle sizes of 1μm-5μm. As a result, the Examiner maintains that because Meade teaches a triple combination and given that Meade teaches that the size of the active substances of the triple combination are most preferably in a range from 1μm-5μm, the Examiner maintains that the low agglomeration exhibited by such particles over time as demonstrated by applicant would

necessarily come about in the particles of Meade. Consequently, the Examiner contends that the unexpected results purported by applicant are neither unobvious nor unexpected.

As for applicant's arguments that Keller is concerned with poor moisture problems and that Keller is not directed to any particular combination, such arguments have been fully considered but are not found persuasive. The Examiner again reminds applicant that the claims are directed to a composition and not to a method of treatment and therefore do not need to have the same utility as the instant invention. Thus, if the prior art composition contains the exact same components as applicant; the Examiner contends that such components would necessarily be capable of achieving the same function as that of applicant, i.e. treatment of respiratory diseases in this case. As for applicant's arguments that Keller does not teach any particular combination of active ingredients, the Examiner again disagrees with applicant since Keller teaches the use of magnesium stearate in dry powder formulations which contain the preferred combination of a beta-mimetic and/or an anti-cholinergic and/or a corticosteroid (see col. 5, lines 52-54). Examples of active substances include a finite number of beta-mimetics such as salmeterol or salts thereof, examples of anti-cholinergics include a finite number of active substances such as tiotropium or tiotropium bromides, and examples of corticosteroids include a finite number of active substances such as fluticasone or fluticasone propionate (see col. 3, lines 58-67). Moreover, Keller et al. teach that the active substance particles possess a mean particle diameter at most of 5

μm. As a result, the Examiner contends that Keller did indeed render obvious applicant's invention as previously claimed. While applicant recites the limitation that 95% of particles are less than 2.5 μm and that the remaining particles had a size between 2 μm to 5 μm, the Examiner maintains that the claims are still rendered obvious as Keller recited that the active substances (i.e. all or 100% of the triple combination of the active agents possess no more than 5 μm and this reads on approximately 95% of the active substances) are at most 5 μm. As a result, the Examiner maintains that absent unexpected results, one skilled in the art would have reasonably concluded that all of the particles are reduced in size as suggested by Keller. Moreover, the Examiner contends that in light of the fact that Keller teaches the exact same components as applicant's and overlapping particle size, the Examiner maintains that Keller still render obvious applicant's invention.

For the foregoing reasons, the rejections of record under 103 (a) were indeed proper. However, in view of applicant's amendment, the following modified ODP and 103 (a) Final rejections are being made.

***Provisional Non-Statutory Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory

obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-4, 8, 15-18, 20-22, and 24-25 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-3, 5-7, 9-10, and 12-13 of copending Application No. 11/574902 (hereinafter Lulla US Patent Application No. '902) in view of Meade et al. (U.S. 2003/0018019 A1, previously cited). Although the conflicting claims are not completely identical, they are not

patentably distinct from each other because both applications are directed to a formulation comprising beta-mimetics such as salmeterol and anti-cholinergics such as tiotropium administered via inhalation or metered dose inhaler for the treatment of COPD.

While the co-pending application Lulla '902 does not teach addition of corticosteroids or specific particle sizes, Meade et al. teach the combination of beta-mimetics such as salmeterol and anticholinergics such as tiotropium in combination with corticosteroids such as fluticasone for the treatment of COPD and that particles can be in a size between 1 and 5 µm, a range that overlaps applicant's particle size. Consequently, one of ordinary skill would have found it obvious to add corticosteroids to the composition of Lulla '902 since Meade et al. teach their effective combination in the treatment of COPD. Thus, the aforementioned claims of the instant application are substantially overlapping in scope as discussed hereinabove and are prima facie obvious over the cited claims of corresponding application No. 11/574,902.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

**Claims 1-9 and 15-26 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Meade et al. (2003/0018019 A1, previously cited) in view of Foulds et al. (Pharmaceutisch Weekblad Scientific Edition, 1983, Vol. 5, pgs. 74-76, previously cited).**

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

*It is respectfully pointed out that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the limitation of the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See In re Casey, 152 USPQ 235*

*(CCPA 1967) and In re Otto, 136 USPQ 458, 459 (CCPA 1963). Thus, the intended use for the treatment of conditions is not afforded patentable weight.*

Meade et al. teach novel pharmaceutical compositions based on anticholinergics, corticosteroids, and beta-mimetics (see abstract and pg. 1, paragraph 0001). Within the scope of the invention the term anticholinergics 1 denotes salts which are preferably selected from among tiotropium and most preferably tiotropium salts (see pg. 1, paragraph 0004). By salts, the present invention encompasses salts of tiotropium including the bromide salt wherein tiotropium bromide is particularly preferred (instant claims 1-2; see pg. 1, paragraphs 0004-0005). Within the scope of the invention, the word corticosteroids (hereinafter 2) denotes compounds selected from a group which includes fluticasone wherein the most preferred compounds including fluticasone (instant claim 1 and 3; see pg. 1, paragraphs 0006). Any reference to salts of corticosteroids includes sodium salts, propionate salts, etc... (instant claim 2; see pg. 1, paragraph 0007). Examples of beta-mimetics (i.e. denoted as 3) which may be used in the present invention include preferred compound salmeterol or its salts including sulfate salts (instant claims 1; see pgs. 1-2, paragraphs 0008-0012). Meade et al. also teach that the three active substances (i.e. 1, 2, and 3) are administered simultaneously in a single active substance formulation or administered successively in separate formulations (instant claim 1-4, 15-16, 20-21, and 24-25; see pg. 1, paragraph 0003). Additionally, Meade et al. teach that beta-mimetics 3 are optionally referred to as beta2-receptor agonists or ß2-agonists (see pg. 2, paragraph 0013). The pharmaceutical

combination of 1, 2, and 3 (i.e. salmeterol, tiotropium and fluticasone; applicant's elected species; instant claims 1-4; pg. 3, paragraphs 0023-0025) are preferably administered by inhalation (instant claim 8) and provided in the form of their enantiomers, mixtures of enantiomers or in the form of racemates, in the form of suitable inhalable powders (instant claims 18 and 22), or inhalation aerosols (instant claim 9; or as a solution-instant claim 23; see pg. 2, paragraphs 0014 and 0020-0022). Additionally, the present invention is administered in a therapeutic effective quantity and administered along with a pharmaceutically acceptable carrier (instant claim 3; see pg. 2, paragraph 0017-0018). The composition can be provided as inhalable powders (instant claim 18) and provided in admixture with excipients such as lactose (instant claims 3 and 19; pg. 5, paragraphs 0032-0035). Moreover, Meade et al. teach that the inhalable powders can be administered by means of metered dose inhalers (instant claim 17; see pg. 6, paragraph 0046 and pg. 7, paragraph 0055), using propellant free inhalable solutions or suspensions of the aforementioned combination (instant claim 23; see pg. 6, paragraphs 0047-0048 and pg. 9, paragraph 0088) or in nebulisers (instant claim 26; see pg. 7, paragraph 0056). Importantly, Meade et al. exemplify the inhalable powder containing tiotropium bromide in an amount of 0.0045% (i.e. anticholinergic %; instant claim 5), fluticasone propionate in an amount of 0.025% (i.e. corticosteroid; instant claim 7), and salmeterol xinafoate in an amount of 0.01% (i.e. B2-agonist; instant claim 6; see pg. 10, paragraphs 0097-0098). Moreover, Meade et al. teach that the micronized active substances 1, 2, and 3 (i.e. 100% of the anticholinergics, corticosteroids, and beta-mimetics) are preferably with an average particle size of 0.5 to

10 μm or most preferably from 1 to 5 μm (instant claims 1 and 3; see pg. 6, paragraphs 0036 and 0045).

Meade et al. do not explicitly teach that applicant's elected species (i.e. combination xii) is a composition wherein approximately 95% of the active particles have a particle size of below 2.5 μm and the remaining particles have a particle size of between 2.5 and 5 μm.

Foulds et al. teach testing of various nebulizers and distribution of drug particles to the lungs (see abstract). Foulds et al. tested 3 nebulizers and found that the Pulmosonic nebulizer was more effective in delivering the drug to the lungs and faster than the other tested devices (see pg. 75, Discussion Section). Importantly, Foulds et al. teach that the explanation for the differences in performance may be due to particle size (see pg. 76, left col.). Specifically, Foulds et al. demonstrated that the Pulmosonic nebulizer contained close to 71% of particles had a particle size less than 4.1 μm thus motivating one of ordinary skill in the art to formulate the composition with drug particles that are smaller in size.

Moreover, the Examiner contends that because Meade et al. are silent on the percentage of particles that are between 1 to 5 μm, reasonable technical reasoning would lead one to assume that 100% (which is approximately 95%) of the particles would fall between 1 and 5 μm, a range that overlaps applicant's invention. Thus, to

one of ordinary skill in the art would have found it obvious to formulate the composition using small particle size since Foulds et al. teach that such requirement is necessary for better deposition in the respiratory tract.

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the composition of Meade as a triple combination since Meade et al. teach the use of salmeterol, fluticasone, and tiotropium for the treatment of COPD. Moreover, one of ordinary skill would have found it obvious to formulate the particles in small particle sizes of 1 to 5 μm since Foulds et al. demonstrated that small particle size was more efficient in delivering the active substances to the respiratory tract.
Thus, given the teachings of Meade and Foulds, one of ordinary skill would have been motivated to combine the beta-mimetic agent salmeterol with the anti-cholinergic tiotropium in combination with the corticosteroid fluticasone as taught by Meade et al. with the reasonable expectation of providing a formulation that is effective in treating COPD.

**Claims 1-9, 15-22, and 24-26 are rejected under 35 U.S.C. 103 (a) as being unpatentable over Keller et al. (U.S. 6,645,466 B1, previously cited) in view of Foulds et al. (Pharmaceutisch Weekblad Scientific Edition, 1983, Vol. 5, pgs. 74-76, previously cited).**

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

*It is respectfully pointed out that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the limitation of the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. See In re Casey, 152 USPQ 235 (CCPA 1967) and In re Otto, 136 USPQ 458, 459 (CCPA 1963). Thus, the intended use for the treatment of conditions is not afforded patentable weight.*

Keller et al. teach enhanced dry powder formulations for inhalation which contain an ineffective pharmaceutical carrier and a finely divided pharmaceutically active compound of inhalable particle size, i.e. having a mean particle diameter of preferably at most 10 μm and in particular at most 5 μm (instant claims 1, 3, 8 and 22; see abstract, col. 4, lines 55-67, and col. 9, lines 8-14). According to Keller, the active compounds in

the formulation can be various compounds that can be administered by inhalation including a beta-mimetic such as salmeterol, an anti-cholinergic agent such as tiotropium, and a corticosteroid such as fluticasone, or a pharmaceutically acceptable derivative or salt thereof wherein the formulations can contain two or more of the aforementioned active compounds (instant claims 1, 3, 15, 20-21, and 24; see col. 6, lines 1-3 and 13-37). Additionally, Keller et al. teach the use of carriers such as lactose in multi-dose dry powder inhalers for improved flow properties and lubricating properties (see col. 3, lines 47-67). Salts or esters of the pharmaceutical compounds can be provided in the form a of salt including bromide, sulfate, propionate, etc...(instant claims 2, 4, 16, and 25; see col. 6, lines 40-50). Additionally, Keller et al. teach the use of magnesium stearate if the formulation contains a beta-mimetic such as salmeterol, and an anti-cholinergic such as tiotropium bromide, and a corticosteroid such as fluticasone bromide (see col., lines 52-66). Additionally, the active compound can range approximately from 0.1%-10% by weight (instant claims 5-7; see col. 7, lines 11-22). All customary carriers used in dry powder inhalation can be used including mono and di-saccharides such as lactose (see col. 8, lines 1-4) and administered in a multi dose dry powder inhaler (col. 9, lines 21-27).

Keller et al. do not exemplify a formulation containing a beta-mimetic, an anti-cholinergic, and a corticosteroid. Similarly, Keller et al. do not teach the composition as an aerosol, in a nebuliser or a metered-dose inhaler. Moreover, Keller et al. do not specifically teach that applicant's elected species (i.e. combination xii) is a composition

wherein approximately 95% of the active particles have a particle size of below 2.5 μm and the remaining particles have a particle size of between 2.5 and 5 μm.

Keller et al., however do teach that the formulations as dry powder inhalers and formulations that can contain two or more pharmaceutically active compounds (see col. 6, lines 13-37). Keller et al. further teach the use of magnesium stearate in dry powder formulations which contain a beta-mimetic, and/or an anti-cholinergic, and/or a corticosteroid or formulations in the form of the compounds' pharmaceutical salts such as salmeterol xinafoate, tiotropium bromide, and fluticasone propionate (applicant's elected species; see col. 6, lines 57-65).

Foulds et al. teach testing of various nebulizers and distribution of drug particles to the lungs (see abstract). Foulds et al. tested 3 nebulizers and found that the Pulmosonic nebulizer was more effective in delivering the drug to the lungs and faster than the other tested devices (see pg. 75, Discussion Section). Importantly, Foulds et al. teach that the explanation for the differences in performance may be due to particle size (see pg. 76, left col.). Specifically, Foulds et al. demonstrated that the Pulmosonic nebulizer contained close to 71% of particles had a particle size less than 4.1 μm thus motivating one of ordinary skill in the art to formulate the composition with drug particles that are smaller in size.

Moreover, the Examiner contends that because Keller et al. are silent on the

percentage of particles that are at most 5 μm, it is assumed that 100% (i.e. approximately 95%) of the particles would fall in a range wherein the particle sizes are at most 5 μm, a range that overlaps applicant's invention. Thus, to one of ordinary skill in the art would have found it obvious to formulate the composition using small particle size since Foulds et al. teach that such requirement is necessary for deposition in the respiratory tract.

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to combine the active compounds disclosed by Keller et al. into a formulation since Keller et al. teach their use in dry powder formulations. Likewise, one of ordinary skill in the art at the time of the invention was made would have found it obvious to formulate the composition as either an aerosol, in a nebuliser or a metered dose inhaler for proper delivery of the composition and given that it is well known in the art to formulate dry powder formulations as aerosols, in nebulizers or in metered dose inhalers. Moreover, one of ordinary skill would have found it obvious to substitute fluticasone for its salts (i.e. fluticasone propionate) given that the substitution of one known element for another would have yielded predictable results. Additionally, one of ordinary skill in the art would have found it obvious to formulate the composition with drug particle sizes lower than 5 μm since Foulds demonstrated that drug particles of smaller sizes are more effective at depositing in the respiratory tract. Thus, given the teachings of Keller and Foulds, one of ordinary skill would have been motivated to combine the beta-mimetic agent disclosed by Keller et al. with the anti-cholinergic

agent, along with the corticosteroid and formulate the preparation in different forms since Keller et al. teach their use in dry powder inhalers for improved moisture resistance with the reasonable expectation of providing a formulation that is effective in moisture resistance.

**Claim 34 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Meade et al. (2003/0018019 A1, previously cited) in view of Finlay (The Mechanics of Inhaled Pharmaceuticals Aerosols, Published in 2001, Chapter 4, pg. 47).**

The Meade reference is as discussed above and incorporated by reference herein. However, Meade does not teach that approximately 95% of the active particles of the combination xii (i.e. elected species) have a particle size below 2.5 μm and that the remaining particles have a particle size of between 2.5 and 5 μm.

Finlay teaches that particle size is an important property of an inhaled aerosol since it strongly affects deposition of inhaled particle in the respiratory tract. Consequently, Finlay teaches that factors that cause a particle to change its size is an important factor to be considered when formulating inhaled pharmaceutical aerosols, propellant-driven metered dose inhalers, and dry powder inhalers since understanding and predicting these size changes are important in optimizing the respiratory tract deposition of such dosage forms (see pg. 47).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the composition of Meade as a triple combination since Meade et al. teach the use of salmeterol, fluticasone, and tiotropium for the treatment of COPD. Moreover, one of ordinary skill would have found it obvious to formulate the particles in small particle sizes since Finlay teaches that particle size is an important factor that affects deposition of inhaled particles in the respiratory tract. Thus, given the teachings of Meade and Finlay, one of ordinary skill would have been motivated to combine the beta-mimetic agent salmeterol with the anti-cholinergic tiotropium in combination with the corticosteroid fluticasone as taught by Meade et al. and formulate them as small particles as taught by Finlay with the reasonable expectation of providing a formulation that is effective in treating COPD and other respiratory diseases.

**Claim 34 is rejected under 35 U.S.C. 103 (a) as being unpatentable over Keller et al. (U.S. 6,645,466 B1, previously cited) in view of Finlay (The Mechanics of Inhaled Pharmaceuticals Aerosols, Published in 2001, Chapter 4, pg. 47).**

The Keller reference is as discussed above and incorporated by reference herein. However, Keller does not teach that approximately 95% of the active particles of the combination xii (i.e. elected species) have a particle size below 2.5 μm and that the remaining particles have a particle size of between 2.5 and 5 μm.

Finlay teaches that particle size is an important property of an inhaled aerosol since it strongly affects deposition of inhaled particle in the respiratory tract. Consequently, Finlay teaches that factors that cause a particle to change its size is an important factor to be considered when formulating inhaled pharmaceutical aerosols, propellant-driven metered dose inhalers, and dry powder inhalers since understanding and predicting these size changes are important in optimizing the respiratory tract deposition of such dosage forms (see pg. 47).

Thus, to one of ordinary skill in the art at the time of the invention would have found it obvious to utilize the composition of Keller as a triple combination since Keller teaches his composition as dry powder inhalers that can contain two or more pharmaceutically active compounds including salmeterol, fluticasone, and tiotropium. Moreover, one of ordinary skill would have found it obvious to formulate the particles in small particle sizes since Finlay teaches that particle size is an important factor that affects deposition of inhaled particles in the respiratory tract. Thus, given the teachings of Keller and Finlay, one of ordinary skill would have been motivated to combine the beta-mimetic agent salmeterol with the anti-cholinergic tiotropium in combination with the corticosteroid fluticasone as suggested by Keller and formulate them as small particles as taught by Finlay with the reasonable expectation of providing a formulation that is effective in treating COPD and other respiratory diseases.

## *Conclusion*

No claims are allowed.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samira Jean-Louis whose telephone number is 571-270-3503. The examiner can normally be reached on 7:30-6 PM EST M-Th.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/S. J. L. /

Examiner, Art Unit 1627

09/27/2010

/SREENI PADMANABHAN/

Supervisory Patent Examiner, Art Unit 1627